Restriction Requirement

Applicant hereby acknowledges the finality of the Restriction Requirement, and the Examiner's statement that claims 8-12 are withdrawn from consideration.

In response to Applicant's traversal of the Restriction Requirement, the Examiner states that "Applicant traverses stating that Groups I and II are not distinct." Office Action of February 27, 2003, page 2, paragraph 1, lines 3-4. It is respectfully submitted that the foregoing Examiner's statement is false: Applicant hereby clarifies that it never stated that Groups I and II are not distinct. Rather, Applicant's traversal is on the grounds that the Examiner: 1) has not properly applied MPEP 803.04 (Restriction - Nucleotide Sequences), 2) has ignored entirely MPEP 803.02 (Restriction - Markush Claims), and 3) has failed to make a *prima facie* Restriction Requirement.

In making the Restriction Requirement final, the Examiner states that Applicant's traversal has been considered and is unpersuasive, however, the Examiner does not address Applicant's grounds for the traversal. Applicant respectfully submits that the Examiner's requirement for restriction has been overcome. Reconsideration of Applicant's grounds for traversal and withdrawal of the finality of the Restriction Requirement are therefore earnestly requested.

Rejection under 35 U.S.C. § 101

Claims 2, 4 and 5 were rejected as claiming unpatentable subject matter under 35 U.S.C. § 101. More particularly, the Examiner maintains that these claims read on wild-type cells, seeds and pollen, since the claimed cells, seeds and pollen were not subjected to a selection step and therefore may not necessarily contain the transgene. Applicant respectfully disagrees with the rejection.

Applicant's claim 1 recites plant cells comprising a polynucleotide that encodes a human acetylcholinesterase. Claim 1 clearly **requires** the claimed subject matter **to include a polynucleotide encoding a human acetylcholinesterase**, such that any composition that does not contain the polynucleotide clearly would fall outside the scope of the claim. Thus, claim 1 cannot encompass wild-type cells, seeds or pollen, as they would not include a polynucleotide encoding a human acetylcholinesterase. Dependent claims 2, 4 and 5, being dependent upon and further limiting independent claim 1, include all of the limitations of claim 1, and thus also cannot encompass wild-type cells, seeds or pollen.

It is respectfully submitted that the rejection is thus overcome. Reconsideration and withdrawal of the rejection of claims 2, 4 and 5 as claiming non-statutory subject matter are therefore respectfully requested.

Rejections under 35 U.S.C. § 112

Claim 6 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. More particularly, the Examiner maintains that the meaning of the terms "physiologically active" (as applied to a human acetylcholinesterase composition) and "tissue type" (as applied to a plant) is unclear. Applicant respectfully disagrees with the rejection.

A claim is indefinite only if the scope of the claim would not be clear to one of ordinary skill in the art. It is respectfully submitted that the terms "physiologically active" (as applied to a human acetylcholinesterase composition) and "tissue type" (as applied to a plant) are well known in the art, as exemplified by their extensive use in the prior art. Further, the term "physiologically active" is additionally clarified by Applicant's detailed specification. See, *e.g.*, Fig. 2 (describing activity); "On a per soluble protein basis, high activity, comparable to a third of the activity present in mammalian brain and five times more than that present in muscles, was registered in several of the lines, including AChE-53, AChE-54, AChE-62 and AChE-68. In these lines, activity was on the order of 100 mU/g leaf tissue (fresh weight)." Specification at page 7, lines 21-25; also see generally page 5, line 25 to page 9, line 17.

It is respectfully submitted that the Examiner has not shown that the claim terms "physiologically active" (as applied to a human acetylcholinesterase composition) and "tissue type" (as applied to a plant) are susceptible to more than one construction. Indeed, one of ordinary skill in the art reading the claims would apply the plain, ordinary meaning of the terms "physiologically active" (as applied to a human acetylcholinesterase composition) and "tissue type" (as applied to a plant) and, guided by the specification, would understand the scope of the claim. Reconsideration and withdrawal of the indefiniteness rejection of claim 6 are therefore respectfully requested.

Contingent upon the Examiner's refusal to withdraw the rejection, Applicant proposes to submit its Declaration under 37 C.F.R. § 132 showing that one of ordinary skill in the art would understand the meaning of the terms "physiologically active" and "tissue type" as recited in claim 6. Therefore, should the Examiner maintain the rejection in the next Office Action, it is respectfully requested that the rejection not be made final.

Claim 14 was rejected under 35 U.S.C. § 112, first paragraph, as lacking an enabling disclosure. More particularly, the Examiner maintains that the specification is merely enabling for expression of human acetylcholinesterase in plant cells, but does not enable expression in non-plant cells (*e.g.*, mammalian, insect, yeast, bacterial). Applicant respectfully disagrees with the rejection.

In making the 112 rejection of claim 14, the Examiner also makes numerous assertions of fact, but cites no authority in support of the factual assertions. If the Examiner's assertions are intended to indicate that the rejection is based on common knowledge in the art or "well known" prior art under MPEP 2144.03, then Applicant traverses the Examiner's assertion.

The test for enablement is whether the disclosure, when originally filed, contained sufficient information regarding the subject matter of the claims as to enable those of ordinary skill in the pertinent art to make and use the invention. The standard is whether the experimentation necessary to practice the invention is undue or unreasonable. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). See also U.S. v. Telectronics, Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.") (emphasis added). A patent need not teach, and preferably omits, what is well known in the art. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies , Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. Thus, the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 219 (C.C.P.A. 1976).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims; the nature of the invention; the state of the prior art; the level of

one of ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). The Examiner's analysis must consider all the evidence related to each of the Wands factors, and any conclusion of non-enablement must be based on the evidence as a whole. In re Wands, 858 F.2d at 740, 8 USPQ2d at 1407.

The general rule on adequacy of disclosure is that disclosure of a single species is adequate support for a generic claim. In re Bowen, 181 USPQ 48, 50 (CCPA 1974). It is well established that a patent applicant is entitled to claim his invention generically, when he describes it sufficiently to meet the requirements of Section 112. *See* Utter v. Hiraga, 6 USPQ2d 1709, 1714 (Fed. Cir. 1988) ("A specification may, within the meaning of 35 U.S.C. §112¶1, contain a written description of a broadly claimed invention without describing all species that claim encompasses."); In re Robins, 166 USPQ 552, 555 (CCPA 1970) ("[R]epresentative samples are not required by the statute and are not an end in themselves."). In In re Rasmussen the court restated the uncontroversial proposition that "a claim may be broader than the specific embodiment disclosed in a specification." 211 USPQ 323, 326 (CCPA 1981).

The Examiner admits that Applicant's disclosure enables expression of human acetylcholinesterase in plant cells. Further, it is respectfully submitted that Applicants are not required to and, in fact, are discouraged from including in their applications that which is already known in the art. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). The expression of human acetylcholinesterase in non-plant cells is known in the prior art. See, *e.g.*, references cited by the Examiner in support of the 102 and 103 rejections of the claims. Applicant's disclosure teaches that expression of human acetylcholinesterase in non-plant cells is known in the art, and further teaches the expression in plant cells, in addition to novel sequences for expression in plant and non-plant cells. Therefore, by reading Applicant's disclosure, combined with the knowledge possessed by one of ordinary skill in the art and the teachings of the prior art, one of ordinary skill in the art would be able to practice the claimed invention (*i.e.*, expression in plant and non-plant cells) without undue experimentation. Reconsideration and withdrawal of the enablement rejection of claim 14 are therefore respectfully requested.

Contingent upon the Examiner's refusal to withdraw the rejection, Applicant proposes to submit its Declaration under 37 C.F.R. § 132 showing that one of ordinary skill in the art would be able to practice the claimed invention (*i.e.*, expression in plant and non-plant cells) without

undue experimentation. Therefore, should the Examiner maintain the rejection in the next Office Action, it is respectfully requested that the rejection not be made final.

Rejections under 35 U.S.C. § 102

Claims 13 and 14 were rejected under 35 U.S.C. § 102 (b) as being anticipated by Soreq *et al.* (U.S. 5,595,903). Claim 13 is amended to overcome the rejection.

Applicant's claim 13, as amended, recites a synthetic polynucleotide comprising a nucleic acid molecule that encodes a human acetylcholinesterase, **wherein said synthetic polynucleotide is modified for improved expression in plant cells**. Soreq (U.S. 5,595,903) does not disclose a synthetic polynucleotide encoding human acetylcholinesterase modified for improved expression in plant cells. Therefore, Soreq does not disclose each and every element of claim 13. It is respectfully submitted that the rejection is thus overcome. Claim 14, being dependent upon and further limiting claim 13, should be allowable for the same reason, as well as for the additional limitations recited therein. Reconsideration and withdrawal of the rejection of claims 13 and 14 as being anticipated by Soreq are therefore earnestly requested.

Claim 15 was rejected under 35 U.S.C. § 102 (e) as being anticipated by Soreq *et al.* (U.S. 5,891,725). Applicant respectfully disagrees with the rejection.

Claim 15 depends from claim 1, which recites one or more **plant cells comprising a polynucleotide encoding a human acetylcholinesterase**. Soreq (U.S. 5,891,725) does not disclose a plant cell comprising a polynucleotide encoding a human acetylcholinesterase. Rather, the reference merely discloses expression in non-plant cells. Therefore, Soreq does not disclose each and every element of claim 15. It is respectfully submitted that the rejection is thus overcome. Reconsideration and withdrawal of the rejection of claim 15 as being anticipated by Soreq are therefore earnestly requested.

Rejection under 35 U.S.C. § 103

Claims 1-7 and 13-15 were rejected under 35 U.S.C. § 103 (a) as being unpatentable over Soreq, as applied to claims 13-15 above, and further in view of Goodman. Applicant respectfully disagrees, and believes the claims, as amended, are patentable over Soreq (both 5,891,725 and 5,595,903) and Goodman, both individually and in combination, for the reasons given above in respect to the section 102 rejections of claims 13-14 and 15. The arguments above as to the novelty of claims 1, 13-14 and 15 are repeated here by reference.

In making the obviousness rejection, the Examiner also asserts that one would have a reasonable expectation of success in making the claimed invention, however, the Examiner cites no authority in support of the factual assertion. If the Examiner's assertion is intended to indicate that the obviousness rejection is based on common knowledge in the art or "well known" prior art under MPEP 2144.03, then Applicant traverses the Examiner's assertion.

It is respectfully submitted that the Examiner has not made a *prima facie* showing of obviousness. More particularly, the Examiner has not shown any evidence in the prior art that suggests one of ordinary skill in the art would have a reasonable expectation of success in expressing active human acetylcholinesterase in plants.

It is well known in the art that expression of foreign genes in plants is highly unpredictable, particularly when the foreign gene is a non-plant gene. For example, Sweetlove *et al.* (1996, Biochem. J. 320:493-498) found no differences in starch content, tuber number, tuber weight, or metabolite content between potatoes transformed with a gene encoding ADP-glucose pyrophosphorylase and potatoes from control plants, even though the activity of the enzyme was four-fold higher in the transformed plants (page 495 and page 497, right column, paragraph 3). Further, Thiele *et al.* (1999, Plant Physiol. 120:73-81) teach that in potato plants transformed with the *Arabidopsis phytochrome* B gene, the endogenous phytochrome B transcript levels were not significantly affected (page 75, right column, paragraph 3, and Fig. 1). Furthermore, genes encoding proteins thought to be directly involved in disease resistance may be ineffective in conferring disease resistance, following their expression in transgenic plants (see, *e.g.*, Linthorst *et al.*, page 285, Abstract), or may fail to confer protection (see, *e.g.*, Dandekar *et al.*, page 15 1, Abstract). Indeed, the prior art as a whole teaches that expression in plants is highly unpredictable. See, *e.g.*, The Plant Cell, vol. 1, 285-291 (1989).

At the time of Applicant's invention, it was unknown whether human acetylcholinesterase could be expressed in plant cells at all, let alone whether the protein would have any activity. For example, it was uncertain whether the protein would be co- and/or post-translationally modified and/or folded properly when expressed in plant cells. Further, it was unknown, for example, whether the codon frequency of the native human gene would allow it to be expressed in plants in therapeutic amounts. These and numerous other factors made it highly unpredictable whether active human acetylcholinesterase could be produced in plant cells. It is respectfully submitted that the rejection is thus overcome. Reconsideration and withdrawal of the obviousness rejection are therefore earnestly requested.

Contingent upon the Examiner's refusal to withdraw the rejection, Applicant proposes to submit its Declaration under 37 C.F.R. § 132 showing that claims 1-7 and 13-15 are non-obvious. Therefore, should the Examiner maintain the rejection in the next Office Action, it is respectfully requested that the rejection not be made final.

Applicant believes the claims, as amended, are patentable over the prior art, and that this case is now in condition for allowance of all claims therein. Such action is thus respectfully requested. If the Examiner disagrees, or believes for any other reason that direct contact with Applicant's attorney would advance the prosecution of the case to finality, he is invited to telephone the undersigned at the number given below.

"Recognizing that Internet communications are not secured, I hereby authorize the PTO to communicate with me concerning any subject matter of this application by electronic mail. I understand that a copy of these communications will be made of record in the application file."

Respectfully Submitted:

By:_____

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APPENDIX OF AMENDED CLAIMS

The following are the claims in this case, as amended to date, showing all changes made by this response, in compliance with 37 C.F.R. § 1.121(c)(1)(ii):

13. (Amended) A synthetic polynucleotide comprising a nucleic acid molecule that encodes a human acetylcholinesterase, wherein said synthetic polynucleotide is modified for improved expression in plant cells.